Tumour Necrosis Factor Inhibitor monotherapy versus combination therapy for the treatment of psoriatic arthritis: combined analysis of European biologics databases

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Conflict of interest

NM, AN, RC, MT and CC report grants from Pfizer during the conduct of the study. NM reports personal fees from AbbVie and Lilly and grants from Lilly outside the submitted work. CC reports grants from Celgene, Lilly and Novartis and personal fees from Novartis outside of the submitted work. FI reports personal fees from Abbvie, BMS, Novartis, Pfizer, Lilly, UCB and MSD outside the submitted work. GL reports personal fees from AbbVie, BMS, Novartis, Pfizer and MSD outside the submitted work. KP reports honoraria for consultations and speakers fees from AbbVie, Pfizer, UCB, Lilly, Novartis and Roche outside the submitted work. PS reports that the Hellenic Registry for Biologic Therapies" was supported in part by the Hellenic Rheumatology Society through unrestricted grants from Schering-Plough, AbbVie, Pfizer, Bristol Myers Squibb and Roche during the conduct of the study. These companies had no role in study design, collection, analysis and interpretation of the data and in the writing of the manuscript. PS also reports grants and personal fees from the pharma industry through the "University of Crete Special Account for Research", outside the submitted work. AD, IF, RH, SL, BM, RM, MN, AS, GS, LS, MU and JZ, have nothing to disclose.

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Short running head

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Abstract

Objective

To investigate whether tumour necrosis factor inhibitor (TNFi) combination therapy with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) is more effective for psoriatic arthritis (PsA) and/or improves TNFi drug survival compared to TNFi monotherapy.

Methods

Five PsA biologics cohorts were investigated between 2000 and 2015; the ATTRA registry (Czech Republic), the Swiss Clinical Quality Management PsA registry, the Hellenic Registry of Biologics Therapies (Greece), the University of Bari PsA biologics database (Italy) and the Bath PsA cohort (UK). Drug persistence was analysed using Kaplan-Meier and equality of survival using Log-Rank tests. Comparative effectiveness was investigated using logistic regression with propensity scores. Separate analyses were performed on: (a) the combined Italian/Swiss cohorts for change in rate of DAS-28; and (b) the combined Italian, Swiss and Bath cohorts for change in rate of HAQ.

Results

In total, 2294 patients were eligible for the drug survival analysis. In the Swiss (p=0.002), Greek (p=0.021) and Bath (p=0.014) databases patients starting TNFi in combination with MTX had longer drug survival compared to monotherapy, whilst in Italy the monotherapy group persisted longer (p=0.030). In patients from the combined Italian/Swiss dataset (n=1066) there was no significant difference between treatment arms in rate of change of DAS28. Similarly, when also including the Bath cohort (n=1205) there was no significant difference in rate of change of HAQ.

Conclusion

Combination therapy of a TNFi with a csDMARD does not appear to affect improvement of disease activity or HAQ versus TNFi monotherapy but may improve TNFi drug survival.

Introduction

Tumour necrosis factor inhibitors (TNFi) are an effective treatment for psoriatic arthritis (PsA)[1] and are generally prescribed following the failure of initial treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), of which methotrexate (MTX) is the most widely used. TNFi may be prescribed as monotherapy or in combination with csDMARDs with between 51% and 79% of patients using TNFi in combination with MTX.[2] A systematic review of randomised controlled trials (RCTs) and observational studies of TNFi monotherapy versus TNFi combination therapy with MTX did not find any difference in efficacy for peripheral disease but there was some evidence of benefit of combination therapy on TNFi drug survival.[2] Whilst there is clear evidence for the benefit of combination TNFi plus csDMARDs in rheumatoid arthritis (RA),[3] the value of combination therapy in PsA remains unresolved,[4] and this may explain the variability observed in clinical practice, and the lack of clarity in current treatment guidelines. [5, 6]

Biologics registries have been set up globally to investigate the long-term efficacy and safety of TNFi. The aim of this study was to combine data from multiple European TNFi databases to describe the utilisation patterns of TNFi monotherapy and combination therapy in PsA and investigate the comparative effectiveness of TNFi monotherapy versus combination therapy in terms of drug survival and patient outcomes.

Materials and methods

Participating databases

An invitation to participate in the study was sent to all European biologics registries known to collect data on patients with PsA. Three biologics registries and two hospital-based PsA biologics cohorts agreed to participate and were included in the study: The ATTRA registry, Czech Republic (the 'Czech database'); The Swiss Clinical Quality Management (SCQM) in Rheumatic Diseases PsA registry, Switzerland (the 'Swiss Database'); the Hellenic Registry of Biologics Therapies (HeRBT), Greece (the 'Greek Database'); the University of Bari School of Medicine PsA biologics database, Italy (the 'Italian Database'); and the Royal National Hospital for Rheumatic Diseases, Bath, UK PsA cohort (the 'Bath Database'). The hospital-based Italian and Bath databases are both prospective cohort studies that have submitted data to the Italian GISEA biologics registry and the British Society for Rheumatology rheumatoid arthritis biologics registry (BSRBR-RA) respectively and were therefore deemed of sufficiently high quality in terms of data collection to be included in the study. Ethics approval was granted for each of the five cohorts (for the lead centre this was by the South West-Central Bristol NRES Committee – approval number BA74/00-01, all other approvals can be found in Supplementary Table 1). A summary of data collection for each database is shown in Supplementary Table 2.

Study population

The study period ran from 01-Jan-2000 to 31-Dec-2015. We included all adults (≥18 years) with a clinical diagnosis of PsA who were new (first line) users of TNFi during the study period, and who were registered in their respective biologics database from the time of first TNFi prescription. Patients who had been prescribed any other type of biologic DMARD before their first TNFi prescription were excluded. Patient and disease characteristics at baseline were extracted from the databases.

Drug exposure and patient follow-up

Recorded prescription data was used to determine exposure status during the follow-up period. Exposure to treatment groups was classified at baseline into: TNFi monotherapy, TNFi

combination therapy with MTX and this group was also included in a category of TNFi combination therapy with any csDMARD (including MTX).

Patient follow-up and outcome measures

Patients were followed until their censoring date, which was the earliest of (a)the time of discontinuation of their first TNFi agent, defined as discontinuation of therapy for at least three months; or (b)the date that they were lost to follow-up; or (c)the date of their last follow-up on the biologics database whichever was the earliest. Drug persistence was defined as the time from TNFi to censoring date.

The primary outcome measure for the comparative effectiveness analyses was rate of change of disease activity, measured using the 28-item Disease Activity Score (DAS28),[7] during the follow-up period. The secondary outcome measure was rate of change in physical function, measured using the Health Assessment Questionnaire (HAQ),[8] during the follow-up period.

Statistical analyses

Statistical analyses were undertaken using R statistical software.[9] Individual patient data from the Bath, Italian and Swiss databases were analysed at the University of Bath, the Czech and Greek data were analysed locally. A full description of the statistical methods can be found in the Supplementary material.

Drug survival

Drug survival was analysed using Kaplan-Meier survival estimates and defined as time from TNFi initiation to censoring date, stratified by treatment group, age at TNFi initiation and sex. The median time from baseline to discontinuation of first TNFi, with 95% confidence intervals (CI_{95}), was calculated from the survival function. The equality of the survival functions was compared using Log-Rank tests.

Comparative effectiveness

Due to the complexity of the comparative effectiveness analyses modelling, we only included data for which we had individual patient data at the University of Bath (Bath, Italian and Swiss

databases). Initial data analysis included examining changes in DAS28 and HAQ over time, without adjustment for covariates.

Comparative effectiveness analyses were based on an intention-to-treat analysis approach using Negative Binomial regression. Comparisons were made between TNFi monotherapy and (a) any TNFi plus csDMARD and, as a sub-group analysis we also compared to (b) TNFi+MTX. For HAQ, in order to allow for the observed excess of zeros, a zero-inflated Negative Binomial model was used, with a consistent set of covariates used for both components of the model. Statistical comparisons were based on the relative difference in *rates of change* in disease score between treatments.

Whilst each registry had planned follow-up periods (for example 3, 6, 12 months), the actual dates of follow-up varied substantially around these, with additional follow-up appointments also being recorded. Attempting to classify these variable follow-up appointments into specific follow-up periods (e.g. change at 3 months, 6 months) resulted in significant loss of data. Therefore, we included all follow-up data in the analysis rather than planned time points.

The regression models were adjusted for age at TNFi initiation and sex. Differences between rates of improvement in the two treatment groups were obtained by including an interaction term between time and treatment group in the regression models. To account for any confounding by indication, we developed database-specific propensity score models, using all available baseline data, to calculate the individual propensity scores for treatment to monotherapy or combination therapy. All covariates, that were not explicitly included in the model, were included in the propensity score models, including clinical characteristics such as disease duration.

Missing values in any explanatory variable (where <70% were missing) were estimated using multiple imputation using the Amelia II package in R.[10] In order to test for a significant difference in the rate of change for each treatment group, estimates of the log Relative Risk (RR) with standard error associated with the interaction between treatment group and time

were extracted and then combined to give an overall estimate of RR, together with a combined standard error using Rubin's rule.

Results

There were 2294 eligible patients identified from the contributing databases, of which 34% started treatment as monotherapy and 66% as combination therapy. Table 1 summarises requirements for access to TNFi and baseline patient characteristics. Clinical guidelines for access to TNFi differed across countries. The impact of the guidelines on measures of disease severity and activity at TNFi initiation was reflected in the relatively lower HAQ and DAS28 scores in the Swiss database and higher baseline scores in the Bath database. Comorbidity data were not consistently recorded across all of the databases, however, in general the proportion of patients with significant comorbidities was <5% of each study population, with the exception of a prevalence of latent tuberculosis of 13% in the Italian database due to screening for latent TB.

Drug utilisation

In all centres, TNFi were more commonly prescribed in combination with a csDMARD than as monotherapy and MTX was the csDMARD most frequently prescribed (Table 1). Changes in baseline prescribing during the study period are shown in Supplemental Figure 1. Patient characteristics and baseline disease activity and severity were generally similar across treatment groups within the databases (Table 1). Adalimumab and etanercept were the most frequently prescribed TNFi in all databases other than the Greek database, where 47.8% of patients were treated with Infliximab. Supplemental Table 3 shows the TNFi products prescribed at baseline. The majority of patients (81.7% monotherapy and 66.0% combination therapy) did not have changes to their baseline treatment regimen before discontinuing their first TNFi, and >85% of these changes were made > 12 months after TNFi initiation.

Drug survival

The Kaplan-Meier survival curves for drug survival on first TNFi, stratified by database and baseline treatment regimen, are shown for monotherapy versus any csDMARD combination

therapy in Figure 1 and monotherapy versus combination therapy with MTX in Supplemental Figure 2. Figure 2 shows the Kaplan-Meier survival curves for drug survival stratified by sex and supplemental Figure 3 shows them stratified by age. Median survival times are shown in Table 2. Discontinuation of first TNFi was earliest in patients in the Swiss database (median 2.8 years, (CI_{95}1.5-3.7)); patients in the Greek database had the longest median survival time (6.9 years, (CI_{95}4.9, NA)).

In all but the Italian database, patients on combination therapy had longer survival on their first TNFi than those on monotherapy. This ranged from 0.5 to 2.9 years and the difference was statistically significant in the Bath and Swiss databases for any combination and in the Bath, Greek and Swiss databases for combination with MTX (Figure 1, Table 2). In the Italian database, patients on monotherapy persisted significantly longer on their first TNFi than those on combination therapy, but this difference did not remain significant when the analyses were limited to combination therapy with MTX. In all but the Czech database, where we observed no difference, men persisted significantly longer on their first TNFi than women (Figure 3, Table 2).

Comparative effectiveness

The analysis of rate of change in DAS28 included 1056 patients from the Swiss and Italian databases with a DAS28 score recorded; 441 were prescribed TNFi monotherapy at baseline and 615 were prescribed combination therapy with any csDMARD, of whom 442 were prescribed TNFi+MTX. Sixty-eight patients from the Swiss database were excluded because they did not have a DAS28 score recorded. The analysis of rate of change in HAQ included 1205 patients from the Bath, Swiss and Italian databases (504 monotherapy, 701 combination therapy with any csDMARD of whom 505 were exposed to TNFi+MTX). We excluded 107 Swiss patients and 11 Bath patients who had no HAQ scores recorded before their censoring dates.

Within the database-specific propensity score models for both the DAS28 and HAQ analyses, patients who had previously used csDMARDs had a higher baseline HAQ and those who had a history of dactylitis were significantly more likely to be prescribed combination therapy. None of the recorded comorbidities were significant in the models and there was no difference in the propensity scores for TNFi plus any csDMARD and TNFi-MTX groups. None

of the variables included in the Bath propensity score model were significantly associated with treatment allocation.

Figures 3 and 4 show the change in DAS28 and HAQ over time, unadjusted for any covariates. In both the DAS28 and HAQ analyses, patients on combination therapy had higher baseline scores than patients on monotherapy. The pattern of *rate of change* was similar in both analyses with scores dropping sharply in the first year after treatment initiation, increasing slightly then stabilising from 12 months onwards.

There was no statistically significant difference in rate of change of DAS28 between patients on TNFi monotherapy with those on combination therapy with any csDMARD (combined Relative Risk (RR_{adj}) 0.98 (CI_{95} 0.95-1.03)) or on monotherapy compared with TNFi+MTX (combined RR_{adj} 0.98 (CI_{95} 0.95-1.02)). There was no statistically significant difference in rate of change of HAQ in patients on monotherapy compared to those on combination therapy with any csDMARD (combined RR_{adj} 1.02 (CI_{95} 0.98-1.06)) or when compared to those on TNFi+MTX (combined RR_{adj} 1.02 (CI_{95} 0.99-1.07)). Inclusion of the propensity scores in the models did not significantly change the combined RRs.

There were no notable differences in reasons for stopping first TNFi between the databases. Supplementary Table 4 summarises the reasons for treatment discontinuation stratified by database and baseline treatment regimen. Overall 23.5% of the 1323 patients from the Bath, Italian and Swiss databases discontinued treatment in the first year after TNFi initiation and the proportion was lower in patients exposed to TNFi+MTX (21.8%) than those on monotherapy (25.9%) or TNFi+non-MTX csDMARD (26.5%). Lack of treatment efficacy was the most frequently recorded reason for discontinuation (9.8% overall, 11.3% monotherapy, 7.9% TNFi+MTX and 10.8% TNFi+non-MTX csDMARD) followed by adverse drug reactions (7.6% overall, 7.0% monotherapy, 6.5% TNFi+MTX and 9.4% TNFi+non-MTX csDMARD). Lack of treatment efficacy remained the most frequently recorded reason for treatment discontinuation at any time after TNFi initiation followed by adverse drug reactions.

Discussion

The results of this multi-registry study are consistent with previous studies of TNFi monotherapy versus combination therapy treatment in patients with PsA. We found no significant difference in clinical outcome between the treatment groups, which is in line with observational studies in Sweden,[11] Norway,[12, 13] the UK,[14] Denmark[15] and Finland.[16] A recent randomised controlled trial found that combination therapy of etanercept and methotrexate may not improve radiographic progression compared with etanercept monotherapy, although combination therapy had slightly greater efficacy for dermatologic end points.[17] In the Bath, Greek and Swiss databases, patients were found to persist significantly longer on their first TNFi when prescribed in combination with MTX than patients on TNFi monotherapy. This has also been observed in studies in Denmark,[15, 18] Norway,[13] Sweden[11] and Italy;[19, 20] in Denmark, however, this was only found when adjustments were made for other baseline variables.[15] Although some studies have not reported significantly longer persistence with MTX,[16, 21, 22] no study has reported longer persistence for patients on monotherapy as was observed in the Italian database. One study in the US, however, did report different findings for the individual TNFis, with significantly longer persistence for etanercept as monotherapy although the opposite was observed for infliximab and there was no difference between treatment groups for adalimumab.[22] Our study, however, did not look at individual TNFis so could not determine whether the benefit of combination therapy varied by TNFi. Our study did find some evidence that a lower proportion of patients on TNFi+MTX stop in the first year of treatment due to lack of treatment efficacy or adverse drug reactions. The reason for this finding is not clear and whether there is an explanatory biological mechanism such as the inhibition of the development of anti-drug antibodies needs further investigation.

A study in Sweden had found patients without MTX showed significantly lower drug survival due to adverse events but did not find a difference for treatment failure.[11] Our study found that, in all but the Czech database, males persist significantly longer on their first TNFi than females which has been observed in some studies looking at PsA [15, 19-21, 23-26] but not others.[11, 13] This finding has also been reported for RA and ankylosing spondylitis.[27-29] Other predictors that have been found to be associated with drug survival include having a higher baseline CRP,[11, 15] a low baseline VAS score for global health,[15] being a non-smoker[13] and

absence of baseline comorbidity,[21, 26, 30] including a metabolic syndrome related co-morbidity,[31] and obesity.[32] Predictors have also been reported to vary depending on the reason for discontinuation, with some being associated with discontinuation for adverse events and others for a lack of efficacy.[11, 15]

This study aimed to combine European biologics registry data to investigate treatment utilisation patterns and outcomes in PsA. The prescribing criteria and disease activity scores, however, were not standardised across databases and as such the drug utilisation analyses were carried out separately. For the comparative effectiveness analyses, limitations included the fact that individual patient-level data was not available for all databases and also that HAQ was the only outcome measure commonly recorded. For the databases where individual level data was available and outcome measures were common we have, however, demonstrated that statistical models using individual patient data can be developed to combine data that has been collected in different healthcare contexts but using similar study designs. Although patients from the different databases had differing baseline disease activity and severity scores due to differences in access requirements to TNFi across Europe, we have demonstrated that clinical outcome measures can be combined by analysing rate of change rather than absolute change in DAS28 or HAQ from baseline which was a methodological strength of the study.

Another limitation of the data was that the actual dates of follow-up varied considerably. It was therefore necessary, when performing the modelling for the comparative effectiveness, to include all follow-up data and model time as a continuous covariate, as restricting to specific time periods would have resulted in a significant loss of data and the potential for bias.

We designed the study to use DAS28 as the primary outcome measure and HAQ as the secondary outcome measure because the majority of biologics databases have been set up to primarily collect treatment effectiveness and safety data in patients with RA and we therefore expected that DAS28 would be the outcome measure more readily available. Whilst DAS28 has been validated for use in PsA its usefulness is limited by the exclusion of the ankle joints and feet which are frequently affected in PsA. We did, however, find that all databases

collected data on HAQ, which is arguably a more relevant outcome measure for studies of PsA. However, none of the databases collected data on all of the outcome measures in the more disease specific Outcome Measures for Rheumatology (OMERACT) core set of outcomes for PsA[33]. As a result, our analysis of the effectiveness of TNFi treatment is limited to physical function and cannot take into account other domains important to people with PsA and to cost-effectiveness analyses such as pain, fatigue, work productivity, enthesitis or skin disease activity and health related quality of life.

We used propensity score modelling to attempt to minimise the impact of confounding by indication and channelling bias, however the effectiveness of propensity score adjustment for treatment allocation is limited by the variables collected in the databases and whether they are the variables that might be associated with treatment allocation. We used all available data within the propensity score models and both a history of dactylitis and higher baseline HAQ scores predicted the use of combination treatment. However, there were issues with large amounts of missing data for some variables and we had no measures of previous treatment compliance, tolerance or success. Therefore, we cannot rule out the potential for uncontrolled confounding by indication and it is not possible to predict the impact that this might have on the findings of the study.

In conclusion, we have demonstrated the feasibility of combining biologics registry and database data to investigate the comparative effectiveness of TNFi treatment for PsA but as with all observational studies the results need to be interpreted with caution. We have found that whilst there is no significant difference in treatment outcome, as measured using DAS28 and HAQ, patients on combination therapy persist longer on their first TNFi than those on monotherapy. Gender appears to be a major risk factor in determining TNFi survival, with males persisting for longer.

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Table 1. Patient characteristics stratified by biologics database and baseline treatment regimen

Baseline characteristic	**ATTRA – Czech Republic**			**Bari – Italy**			**Bath – UK**			**HeRBT – Greece**			**SCQM - Switzerland**		
Nº of patients	658 (358 males, 300 females)			300 (140 males, 160 females)			199 (100 males, 99 females)			314 (142 males, 172 females)			824 (407 males, 417 females)		
Criteria for PsA	Moll & Wright to 2012 Moll & Wright or CASPAR from 2012			CASPAR			CASPAR			Clinical diagnosis by a rheumatologist (usually using CASPAR)			Clinical diagnosis by a rheumatologist		
Requirements for starting TNFi	PsA not adequately controlled using csDMARDs			EULAR guidelines: Inadequate response to ≥1 csDMARD			EULAR / BSR guidelines: peripheral arthritis with ≥3 SJC and ≥3TJC and inadequate response to ≥2 csDMARDs			HSR guidelines: peripheral arthritis with ≥3 SJC and ≥3TJC and inadequate response to ≥2 csDMARDs *or* BASDAI >4 and inadequate response ≥2 NSAIDs			No rigid guidelines but generally active disease with inadequate response to ≥1 csDMARD		
Baseline treatment regimen	**Mono**	**Combo any csDMARD**	**Combo MTX**	**Mono**	**Combo any csDMARD**	**Combo MTX**	**Mono**	**Combo any csDMARD**	**Combo MTX**	**Mono**	**Combo any csDMARD**	**Combo MTX**	**Mono**	**Combo any csDMARD**	**Combo MTX**
Number of patients n(%)	141 (21.4)	517 (78.6)	363 (55.2)	110 (36.7)	190 (63.3)	146 (48.7)	86 (43.2)	113 (56.8)	75 (37.7)	77 (24.5)	237 (75.4)	204 (65.0)	363 (44.1)	461 (55.9)	320 (38.8)
Males (%)	48.2	52.2	50.1	51.8	43.8	43.2	46.5	53.1	49.3	61	52.7	53.4	52.3	47.1	48.4
Age at TNFi initiation Median (IQR)	45.0 (37.0; 54.0)	48.0 (39.0; 55.0)	48.0 (38.0; 54.0)	49.5 (38.0,59.0)	48.0 (39.0,56.0)	48.0 (39.0,55.8)	48.0 (40.0,56.0)	51.0 (43.0,61.0)	51.0 (43.5,62.0)	48.0 (37.0,57.5)	51.0 (39.2,59.0)	51.4 (39.0,59.1)	47.0 (38.0,56.5)	48.0 (40.0,56.0)	49.0 (40.0,56.0)
Duration of PsA (years) Median (IQR)	*6.0 (2.3; 11.3)*	*6.9 (2.9; 11.8)*	*6.7 (2.6; 11.9)*	3.0 (1.0, 7.0)	3.0 (1.0, 6.0)	3.0 (1.0, 5.3)	9.0 (4.0,22.0)	12.0 (6.0,19.5)	11.0 (6.0,17.0)	5.5 (1.1,14.4)	5.5 (1.9,11.4)	5.0 (1.5,11.0)	2.0 (0.0,7.0)	3.0 (0.0,7.0)	3.0 (0.0,7.0)
Mean (SD) duration of follow-up (years)	4.0 (3.4)	3.6 (2.8)	3.7 (2.8)	6.4 (3.3)	5.6 (3.4)	5.7 (3.5)	4.6 (3.1)	4.9 (2.6)	4.7 (2.4)	2.6 (2.5)	3.0 (2.0)	3.02 (2.8)	3.8 (3.3)	4.4 (3.3)	4.7 (3.4)
Current smoker (%)	*4.3*	*6.0*	*5.8*	20.0	24.7	21.2	14.0	13.3	14.7	*16.9*	*7.2*	*7.8*	*10.2*	*10.4*	*8.8*

Current non-smoker (%)	*22.0*	*29.4*	*30.0*	80.0	75.3	78.8	72.1	82.3	80.0	*9.1*	*10.1*	*10.8*	*28.7*	*29.1*	*28.1*
Smoking unknown (%)	*73.8*	*64.6*	*64.2*	0.0	0.0	0.0	13.9	4.4	5.3	74.0	82.7	81.4	*61.2*	*60.5*	*63.1*
BMI <25 (%)	19.1	22.4	20.7	29.1	32.1	32.1	9.3	19.5	14.6	*24.7*	*14.3*	*14.2*	33.3	29.5	27.8
BMI 25-29 (%)	19.9	29.0	28.1	38.2	41.6	41.8	37.2	37.2	42.7				28.7	30.2	31.9
BMI ≥30 (%)	14.2	20.5	20.9	30.9	24.7	24.6	40.7	39.8	38.6	*6.5*	*11.4*	*13.2*	18.2	19.1	19.1
BMI unknown (%)	46.8	28.0	30.3	1.8	1.6	1.5	12.8	22.2	4.1	*68.8*	*74.3*	*72.5*	19.8	21.2	21.2
DAS28 Median (IQR)	5.1 (4.2; 5.7)	5.3 (4.7; 6.0)	5.4 (4.7; 6.0)	4.0 (3.2,4.7)	4.1 (3.3, 5.0)	4.1 (3.3, 5.0)	-	-	-	4.1 (2.9,5.2)	5.0 (4.0,6.0)	5.0 (3.9,5.9)	3.2 (2.3, 4.3)	3.5 (2.7, 4.3)	3.5 (2.7, 4.3)
HAQ (mHAQ for Greece) Median[1] (IQR)	1.3 (0.9; 1.8)	1.3 (0.9; 1.6)	1.3 (0.9; 1.6)	0.75 (0.12,1.37)	0.75 (0.25,1.50)	0.88 (0.25,1.50)	1.25 (0.47,1.88)	1.12 (0.62,1.88)	1.12 (0.53,1.88)	*0.82 (0.38,1.13)*	*0.75 (0.25,1.13)*	*0.75 (0.25,1.1)*	0.75 (0.25,1.25)	0.75 (0.25,1.25)	0.62 (0.38,1.12)

Data in *grey italic text* indicates that >50% of the data values were missing. IQR, interquartile range; csDMARD, conventional synthetic anti-rheumatic drug – note that the category 'any csDMARD' includes patient prescribed combination therapy with MTX; EULAR, European League Against Rheumatism TNFi guidelines; BSR, British Society for Rheumatology TNFi guidelines; HSR, Hellenic Society for Rheumatology guidelines; TJC, tender joint count; SJC, swollen joint count; BASDAI, Bath Ankylosing Spondylitis Activity Index; NSAID, non-steroidal anti-inflammatory drug; Mono, monotherapy; CASPAR, Classification of psoriatic arthritis; BMI, Body Mass Index (kg/m^2); DAS28, Disease Activity Score 28 item; HAQ, Health Assessment Questionnaire; mHAQ, modified HAQ [1] Rounded to 2 decimal places

Table 2. Median survival times from TNFi initiation to discontinuation of first TNFi stratified by baseline treatment regimen and database

	ATTRA- Czech Republic		Bari - Italy		Bath - UK		HeBRT - Greece		SCQM - Switzerland	
	n	Median survival time (years) (CI_{95})	n	Median survival time (years) (CI_{95})	n	Median survival time (years) (CI_{95})	n	Median survival time (years) (CI_{95})	n	Median survival time (years) (CI_{95})
All	**658**	**5.9 (4.7, 7.6)**	**300**	**4.9 (4.1, 6.6)**	**199**	**4.8 (3.6, 6.6)**	**314**	**6.9 (4.9, NA)**	**824**	**2.8 (2.5, 3.7)**
Treatment regimen at baseline (combination therapy with any csDMARD including MTX)										
Monotherapy	141	4.8 (3.8, NA)	110	6.9 (4.7, NA)	86	3.2 (1.3, 6.5)	77	4.3 (2.9, 8.3)	363	2.6 (1.7, 3.3)
Combination therapy	517	5.9 (4.7, 7.3)	190	4.3 (3.2, 6.2)	113	6.1 (4.5, NA)	237	7.2 (5.3, NA)	461	3.1 (2.6, 4.7)
p-value*		0.6054		**0.0303**		**0.0105**		0.0609		**0.0288**
Treatment regimen at baseline (combination therapy with MTX)										
Monotherapy	141	4.8 (3.5, NA)	110	6.9 (4.7, NA)	86	3.2 (1.3, 6.5)	77	4.3 (2.9, 8.3)	363	2.6 (1.7, 3.3)
Combination therapy	363	6.3 (4.5, 8.0)	146	4.9 (3.9, 6.6)	75	6.1 (4.5, NA)	204	NA (5.4, NA)	320	4.3 (3.0, 6.3)
p-value*		0.5550		0.0737		**0.0135**		**0.0208**		**0.0020**
Age										
18-49 years	370	6.6 (4.3, 8.9)	157	6.0 (4.1, 8.2)	99	5.1 (3.6, NA)	157	7.2 (4.9, NA)	447	3.8 (2.8, 4.6)
50 years and over	288	5.4 (4.4, 7.6)	143	4.5 (3.4, 6.2)	100	4.8 (3.2, NA)	157	6.9 (4.3, NA)	377	2.2 (1.6, 2.9)
p-value*		0.9958		0.3319		0.7923		0.9289		**0.0089**
Sex										
Female	320	5.7 (4.2, 8.2)	160	3.8 (2.7, 4.9)	99	2.4 (1.6, 6.1)	142	4.3 (2.8, 7.8)	417	2.0 (1.5, 2.7)
Male	338	5.9 (4.6, 8.9)	140	7.0 (5.5, 10.7)	100	6.6 (4.8, NA)	172	NA (5.9, NA)	407	4.2 (3.2, 5.6)
p-value*		0.6075		**0.0036**		**0.0100**		**0.0035**		**<0.0001**

*p-value from Log Rank test to compare the equality of the survival; NA – did not reach 50% drop-out.

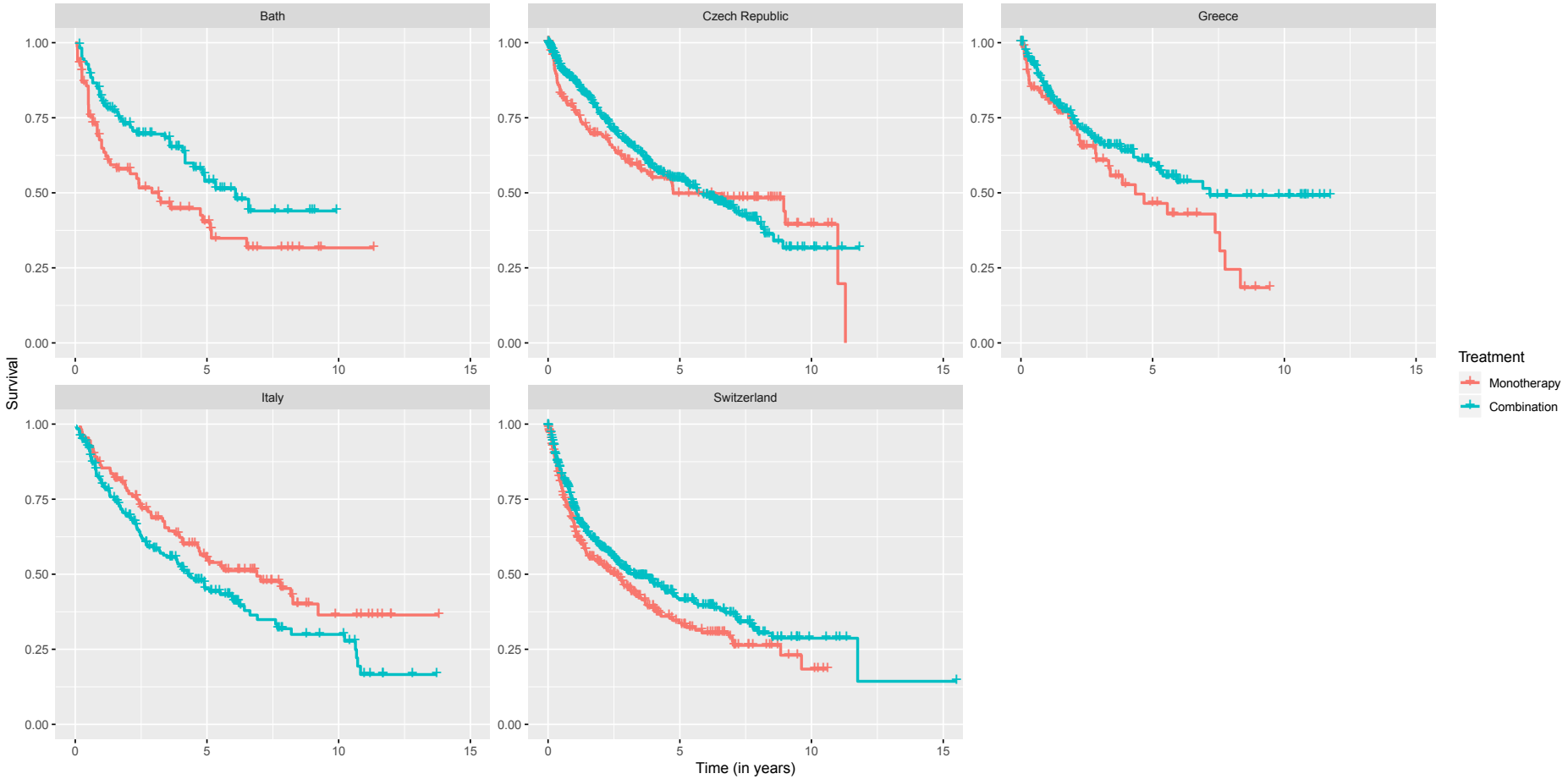


Figure 1. Kaplan-Meier survival estimates from TNFi initiation to discontinuation of first TNFi or data censoring stratified by baseline treatment regimen, monotherapy compared with TNFi + csDMARD combination therapy.

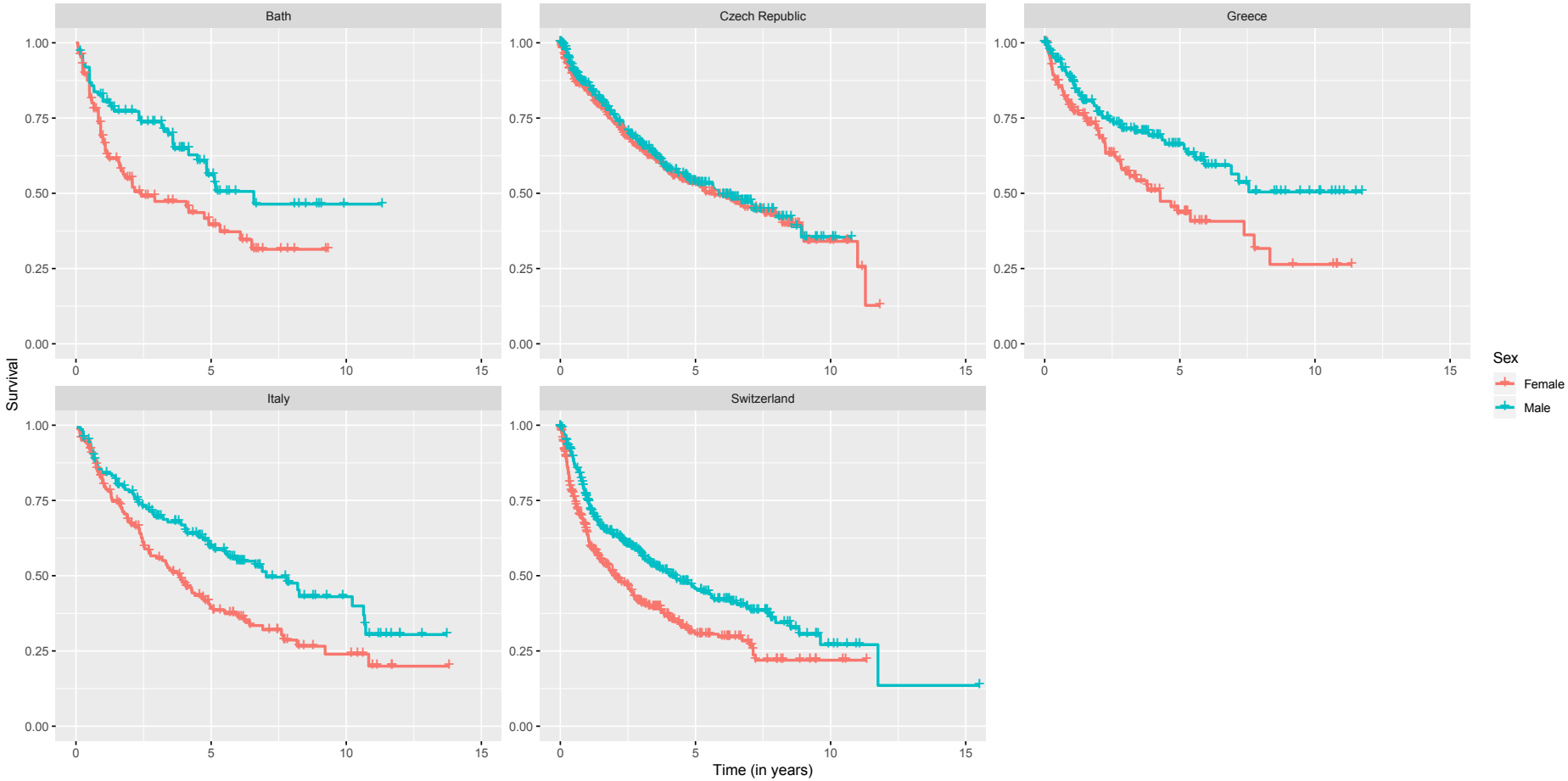


Figure 2. Kaplan-Meier survival estimates from TNFi initiation to discontinuation of first TNFi or data censoring stratified by sex

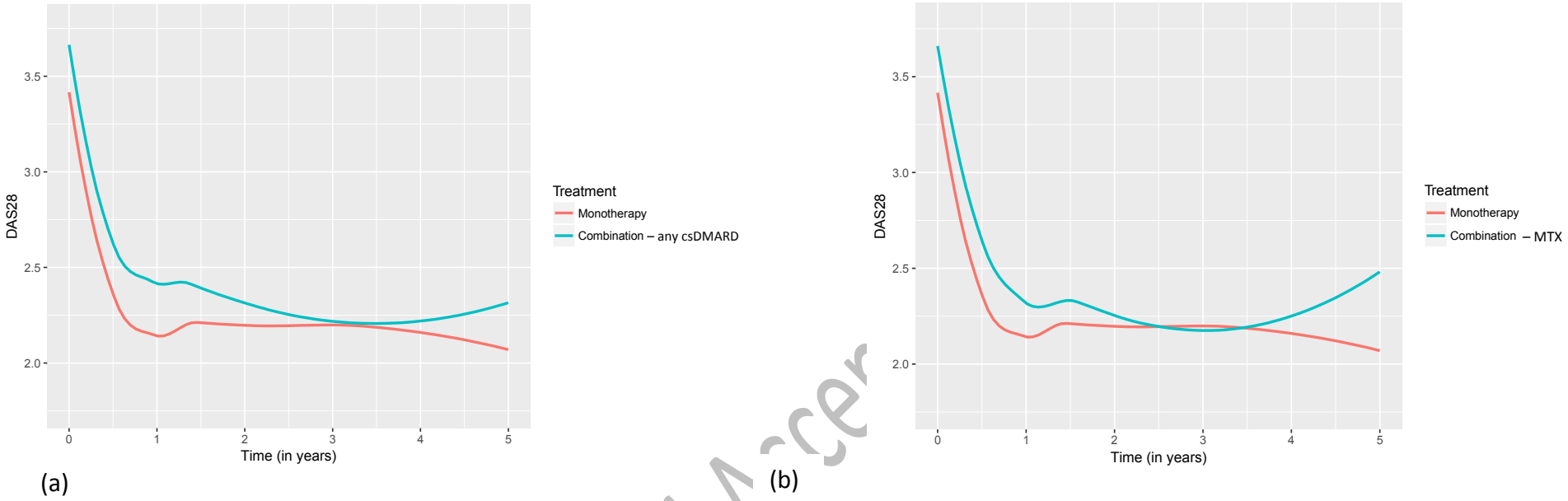


Figure 3. DAS28 over time, unadjusted for any covariates, among patients from the Italian and Swiss databases from TNFi initiation to the earliest of: discontinuation of first TNFi; or date of data censoring; or 60 months follow-up for (3a) monotherapy versus combination TNFi plus any csDMARD and (3b) monotherapy versus combination TNFi plus MTX.

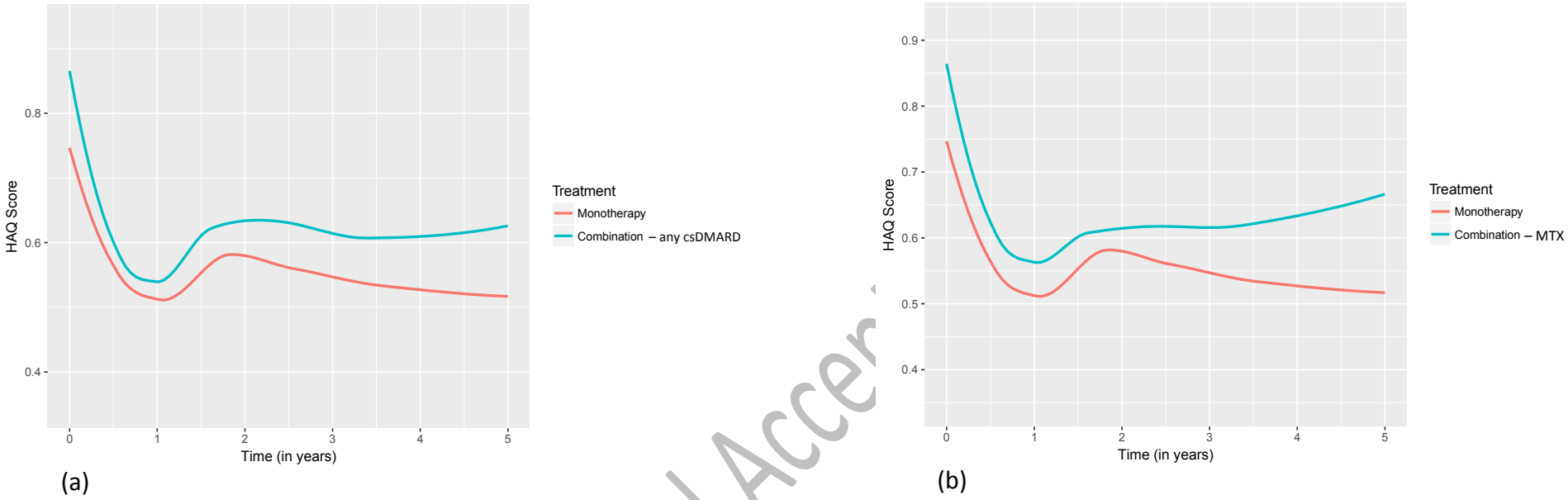


Figure 4. HAQ over time, unadjusted for any covariates, among patients from the Bath, Italian and Swiss databases from TNFi initiation to the earliest of: discontinuation of first TNFi; or date of data censoring; or 60 months follow-up for (4a) monotherapy versus combination TNFi plus any csDMARD and (4b) monotherapy versus combination TNFi plus MTX.

Supplementary material – statistical analysis

Comparative effectiveness analyses

Due to the complexity of the comparative effectiveness analyses modelling, we only included data for which we had individual patient data at the University of Bath (Bath, Italian and Swiss databases). The availability of patient characteristic and outcome data varied between databases and local clinical practice also varied. Initial data analysis included examining changes in DAS28 and HAQ over time, without adjustment for covariates, using non-parametric (loess) smoothers.

Comparative effectiveness analyses were based on an intention-to-treat analysis approach. Patients were followed until their censoring date, which was the earliest of (a) the time of discontinuation of their first TNFi agent, defined as discontinuation of therapy for at least three months; or (b) the date that they were lost to follow-up; or (c) the date of their last follow-up on the biologics database whichever was the earliest. Whilst the formulation of the HAQ and DAS28 means that they are continuous scores, in practice the manner in which they are measured (and rounded), results are typically more categorical in nature (e.g. 84% of the data was grouped in multiples of 0.125). Based on the discretisation observed in the data, HAQ scores were categorised into groups with a width of 0.25 and DAS28 scores into groups with a width of 1. For HAQ, in order to allow for the observed excess of zeros, a zero-inflation model was used with two components. These components represent the two mechanisms through which zeros can be generated (i) a binomial distribution (with a specified probability of generating a zero); and (ii) distribution that represents the observed data (that can also generate zeros). As examination of the outcome showed clear indication that the data were highly skewed and discontinuous, the latter distribution was chosen to be Poisson with allowance for over-dispersion through the use of the Negative Binomial. A consistent set of covariates were used for both components of the model. For DAS28, an excess of zeros was not observed and the Negative Binomial was used. These regression models were used to a compare TNFI monotherapy to (a) any TNFi plus csDMARD and, as a sub-group analysis we also compared to (b) TNFi+MTX, with comparisons based on the relative difference in *rates of change* in disease score between treatments.

Whilst each registry had planned follow-up periods (for example 3 months, 6 months, 12 months), the actual dates of follow-up varied substantially around these dates with additional follow-up appointments being recorded in the databases. Attempting to classify these variable follow-up appointment dates into specific

follow-up periods (e.g. change at 3 months, change at 6 months) resulted in significant loss of data. Therefore, we included all follow-up data in the analysis using the actual follow-up dates rather than planned time points.

Regression models were adjusted for age at TNFi initiation and sex. Differences between rates of improvement in the two treatment groups were obtained by including an interaction term between time and treatment group in the regression models. Whilst we made the assumption that the clinical populations were sufficiently similar in terms of the certainty of diagnosis that their data could be combined, we included indicator variables for each database to account for any potential heterogeneity in the DAS28 and HAQ scores observed between databases.

Clinically, we might expect there to be inherent differences between patients prescribed monotherapy or combination therapy (confounding by indication). If present, these differences would likely result in biased estimates of treatment effectiveness. To account for any confounding by indication observed, we developed database-specific propensity score models, using all available baseline covariate data, to calculate the individual propensity scores for treatment to monotherapy or combination therapy. The cohort-specific propensity score models were then included in the overall pooled model. Using propensity score matching would have resulted in a significant loss of data therefore we included the propensity scores as continuous covariates in the models. The table below shows the variables that were used in each of the propensity score models.

Missing values in any explanatory variable were estimated using multiple imputation using the Amelia II package in R. Variables were removed from the imputation model if they had more than 70% missing values (this only applied to the Baseline Patient Visual Analogue Score in the Bath dataset). The regression and propensity score models were run repeatedly for each imputed dataset. In order to test for a significant difference in the rate of change for each treatment group, estimates of the log Relative Risk (RR) with standard error associated with the interaction between treatment group and time were extracted and then combined to give an overall estimate of RR, together with a combined standard error using Rubin's rule.

Variables included in the propensity score models

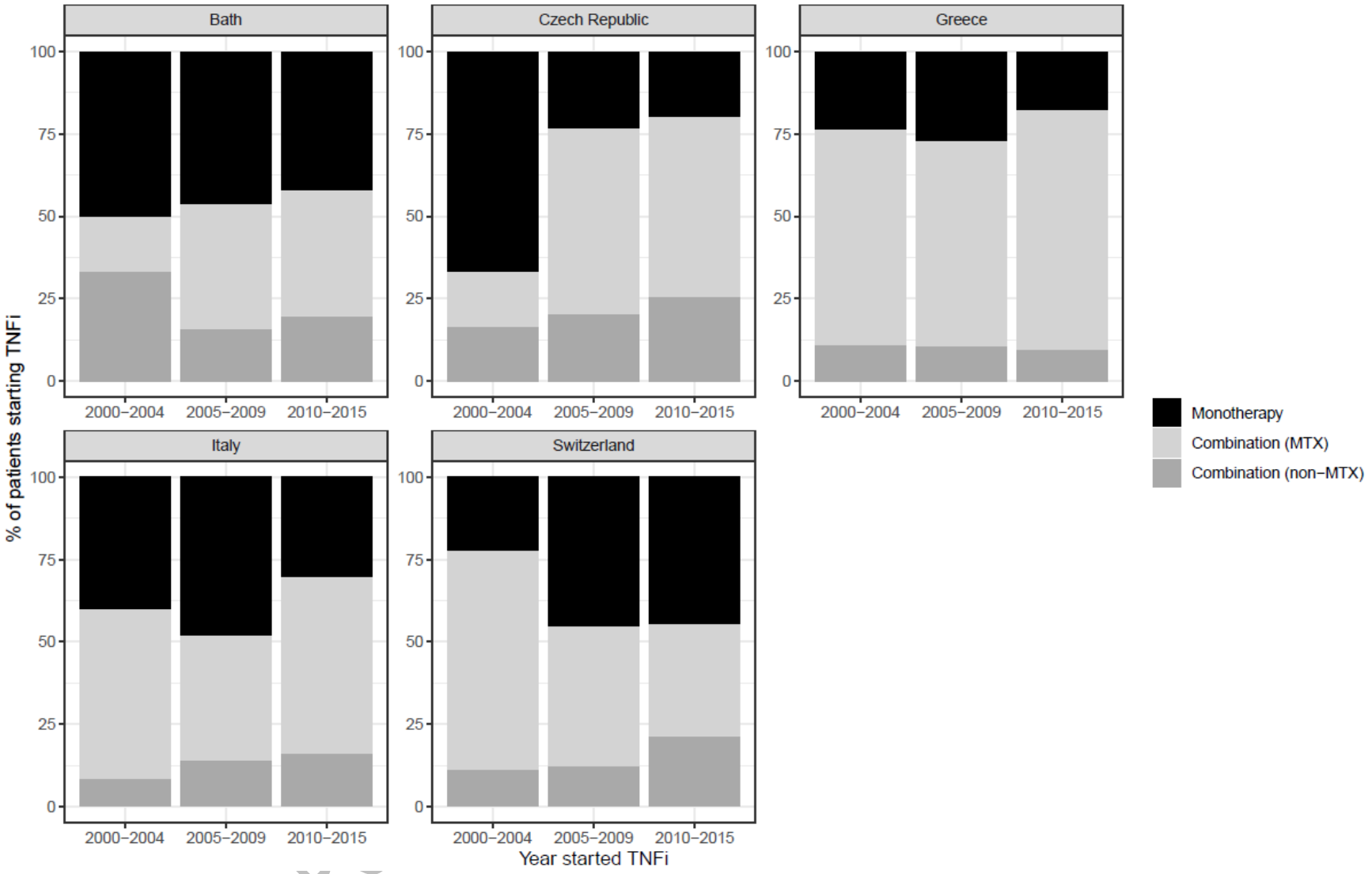
Variable description	Italy	Switzerland	Bath
BMI at baseline	✓	✓	✓
Comorbidities - Psoriasis	✓	✓	✓
Comorbidities - Cardiac Failure	✓	✓	✗
Comorbidities - Malignant Tumour	✓	✓	✗
Comorbidities - Lymphoma	✗[1]	✗[1]	✗
Comorbidities - COPD	✓	✓	✗
Comorbidities - Pulmonary disease	✓	✓	✗
Comorbidities - Chronic hepatopathy	✓	✓	✗
Comorbidities - Tuberculosis	✓	✓	✗
Comorbidities - Inflammatory bowel disease	✓	✗	✗
Comorbidities - Uveitis	✓	✓	✗
Comorbidities - Alcohol Abuse	✗[1]	✓	✗
Comorbidities - Arterial Hypertension	✓	✓	✗
Disease duration at baseline	✓	✓	✓
Previously taken Methotrexate (MTX)	✓	✓	✓
Previously taken DMARDs	✓	✓	✓
Number of previous DMARDs (including MTX)	✓	✓	✓
Name of baseline TNFi	✓	✓	✓
Axial spondyloarthropathy at baseline	✓	✓	✗
Peripheral arthritis at baseline	✓	✓	✗
Enthesitis at baseline	✓	✓	✗
Dactylitis at baseline	✓	✓	✗
Baseline 66 Swollen Joint Count score	✓	✓	✓
Baseline 68 Tender Joint Count score	✓	✓	✓
Baseline Disease Activity Score 28[4]	✓	✓	✗
Baseline Physician Visual Analogue Score	✓	✓[3]	✓
Baseline Patient Visual Analogue Score	✓	✓[3]	✗[2]
Baseline Pain Visual Analogue Score	✓	✓[3]	✓
Baseline Health Assessment Questionnaire Score[4]	✓	✓	✓
Baseline Erythrocyte Sedimentation Rate	✓	✓	✗
Baseline C-Reactive Protein	✓	✓	✗
Baseline EQ5D Score	✗	✓	✓
Baseline Erosions	✗	✗	✓
Hospital Type - Office or Hospital	✗	✓	✗

[1] The data was collected but there were no cases

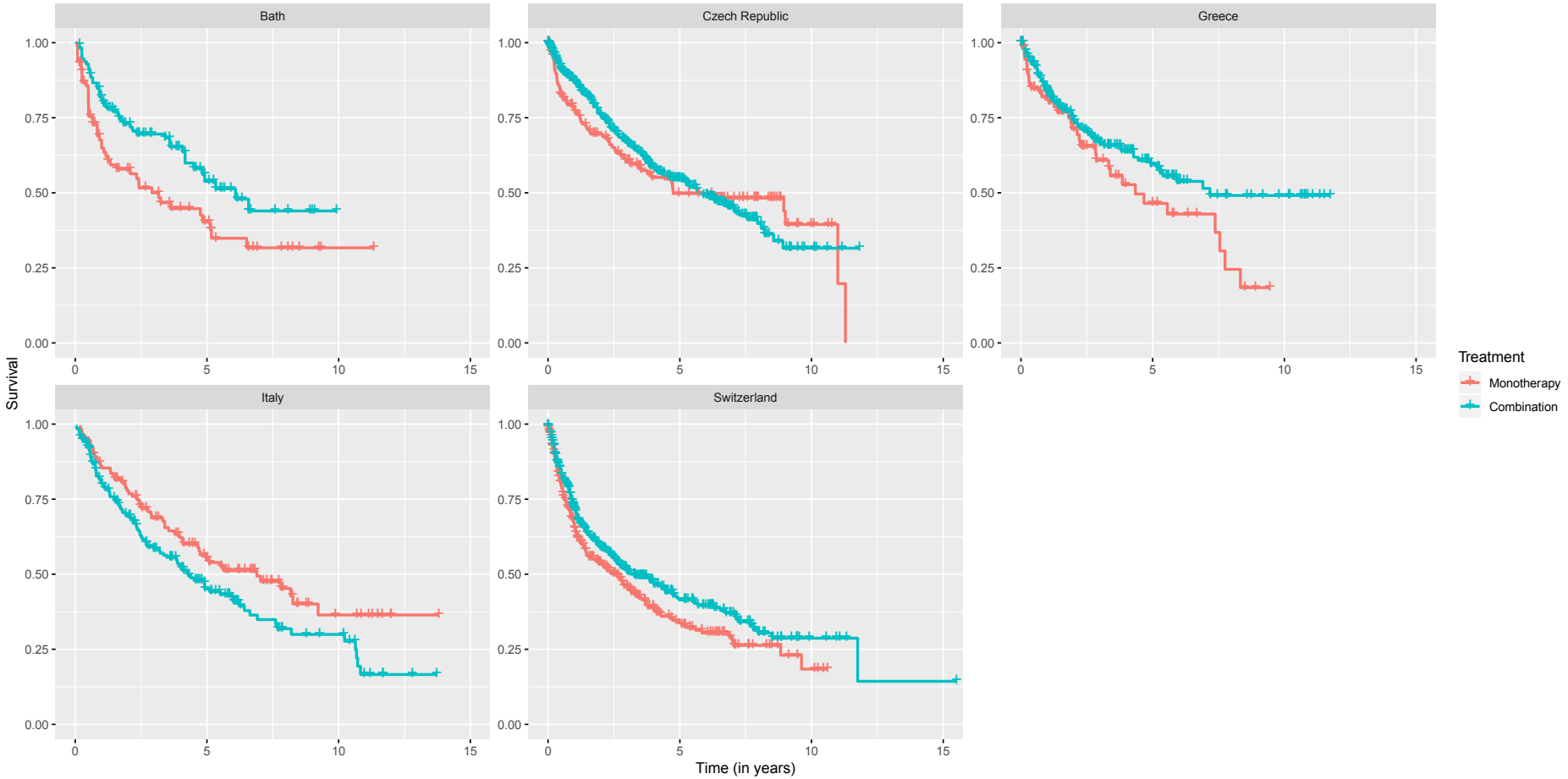
[2] Not included as >70% of the data were missing

[3] Not a VAS but a numerical rating scale

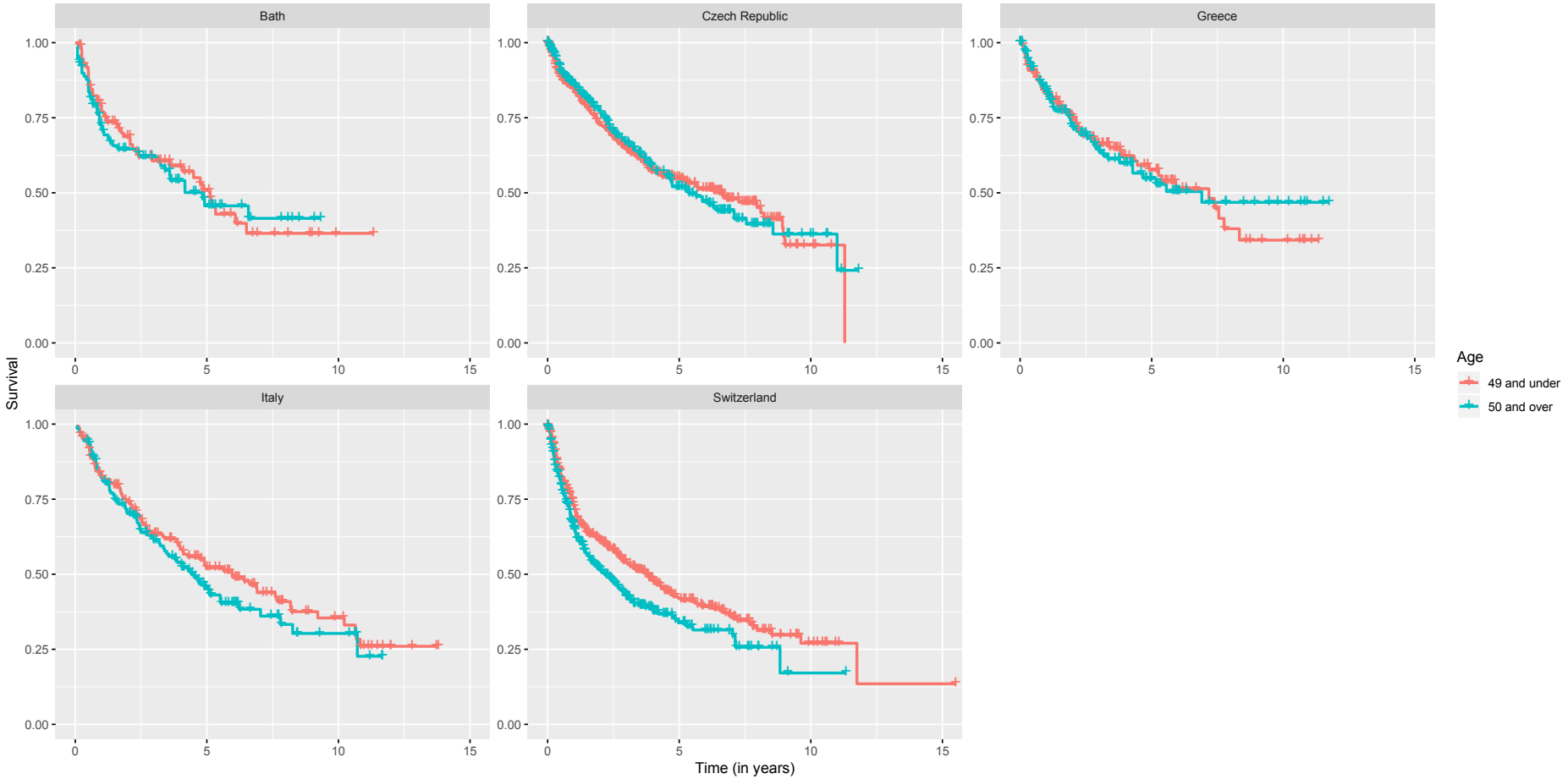
[4] HAQ and DAS28 were not included together – DAS28 was included when looking at HAQ and HAQ was included when looking at DAS28



Supplemental Figure 1: Baseline treatment regimen stratified by database and year of TNFi initiation with combination therapy separated into MTX and other csDMARDs (leflunomide or sulfasalazine).



Supplemental Figure 2. Kaplan-Meier survival estimates from TNFi initiation to discontinuation of first TNFi or data censoring stratified by baseline treatment regimen, monotherapy compared with TNFi + MTX combination therapy.



Supplemental Figure 3. Kaplan-Meier survival estimates from TNFi initiation to discontinuation of first TNFi or data censoring stratified by age.